

Prognosis of a Series of 763 Consecutive Node-Negative Invasive Breast Cancer Patients Without Adjuvant Therapy: Analysis of Clinicopathological Prognostic Factor

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Background and Objectives: The objectives of this study were to confirm the favorable outcome of Japanese invasive breast cancer patients without lymph node metastasis, after treatment with surgery alone, and to evaluate clinicopathological prognostic factors in this population.

Methods: The subjects were 763 consecutive node-negative invasive breast cancer patients who underwent surgery without adjuvant therapies between 1988 and 1993 at our hospital. Disease-free survival (DFS) and overall survival (OS) rates were analyzed by clinicopathological factors.

Results: The median age of the patients at surgery was 52 years and the median follow-up period of patients was 74 months. At 5 years, the respective DFS and OS rates of all patients were 90.8% and 93.9%. Patients with a pathological tumor size of invasive component of more than 2 cm (319 patients) had a significantly lower DFS than those with tumors measuring 2 cm or less (361 patients) ($P = 0.045$). Patients with positive hormone receptor status (280 patients) (estrogen and/or progesterone receptor positive) tended to have a better OS than those negative for both hormone receptors (92 patients) ($P = 0.078$). Meanwhile, patients with tumors of histological grade 3 (328 patients) had a much poorer prognosis than those with tumors of histological grade 1 or 2 (413 patients) ($P = 0.008$ for OS and $P = 0.042$ for DFS). The respective 5-year DFS and OS rates of patients with histological grade 3 tumors larger than 2 cm in pathological tumor size of invasive component (195 patients) were 85.5% and 87.6%, indicating that these node-negative patients form a high risk group.

Conclusions: Japanese invasive breast cancer patients without lymph node metastasis tended to show a survival advantage compared with their Caucasian counterparts. Histological grade was the most useful prognostic factor in this population. *J. Surg. Oncol.* 1999;71:101–105. © 1999 Wiley-Liss, Inc.

KEY WORDS: breast cancer; prognostic factor; lymph node metastasis; histological grade

INTRODUCTION

The prognosis of breast cancer patients with no histological lymph node metastasis, who are treated with surgery alone, remains unclear [1]. The effects of post-

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operative adjuvant therapy on the prognosis of node-negative invasive breast cancer patients are also controversial [1–3]. Until recently, there were no data available on series of consecutive node-negative breast cancer patients who received no adjuvant therapies. In addition, it has been suggested that Japanese breast cancer patients tend to show better survival rates than their Caucasian counterparts [2–5]. This makes it difficult to analyze prognostic factors and the efficacy of adjuvant therapy in node-negative invasive breast cancer patients in Japan.

The purpose of this study was to confirm the better treatment outcome of node-negative invasive breast cancer in Japanese patients compared with their Caucasian counterparts and to evaluate clinicopathological prognostic factors in this population.

SUBJECTS AND METHODS

The subjects of this study were a series of 763 consecutive invasive breast cancer patients without histological lymph node metastasis who were treated between 1988 and 1993 at our hospital. All of these patients were treated with surgery alone and were not given any adjuvant therapy, regardless of tumor size or hormone receptor status. Patients with bilateral breast cancers (synchronous or asynchronous) or second primary malignancies were included in the analyses. All the patients were followed up for at least 5 years. The practicalities of the follow-up procedures have been reported previously [5]. History and physical examinations as well as blood tests were performed at least once every 6 months for 10 years. Blood tests included investigations of liver function and tumor markers (ST-439, CEA, and CA15-3). Chest X-rays, abdominal ultrasound examinations, and bone scintigram scans were performed annually for 5 years. The histological grades of invasive carcinomas were defined as documented previously [6]. Briefly, the histologic grading of the primary tumor was a summed score comprising the degree of structural atypia, the number of mitotic figures, and the degree of nuclear atypia. Individualized cases were categorized as grade 1 when the sum of scores was 3 or 4; grade 2 when the sum was 5, 6, or 7; and grade 3 when the sum was 8 or 9. The number of mitotic figures was counted per 10 high-power fields ($\times 400$). Estrogen receptor (ER) and progesterone receptor (PgR) levels were measured by an enzyme immunoassay [7], with cutoff values of 10 and 13 fmol/mg protein for ER and PgR, respectively. Disease-free survival (DFS) and overall survival (OS) rates were calculated for the entire patient series and also after stratification by the various clinicopathological prognostic factors investigated. All data including pathological and clinical data were retrieved from the patients' medical records. With regard to background factors, complete data were not available for every patient either because some pieces of information were missing or certain tests

TABLE I. Clinicopathological Background Factors for 763 Node-Negative Invasive Breast Cancer Patients

	No. of patients (%)
Menopausal status	
Premenopausal	360 (47.2)
Postmenopausal	370 (48.5)
Unknown	33 (4.3)
Tumor size	
T0	17 (2.3)
T1	255 (33.4)
T2	314 (41.1)
T3	20 (2.6)
T4	4 (0.5)
Tx ^a	153 (20.1)
Operation mode	
Modified radical	591 (77.4)
Standard radical	113 (14.8)
Extended radical	34 (4.5)
Partial resection	25 (3.3)
Histopathological type	
Invasive ductal	658 (86.3)
Mucinous	36 (4.7)
Invasive lobular	27 (3.5)
Medullary	15 (2.0)
Other special types	27 (3.5)
Pathological tumor size of invasive component (t)	
t \leq 2.0 cm	361 (47.3)
t > 2.0 cm	319 (41.8)
Unknown	83 (10.9)
Lymphatic invasion by tumor cells	
Positive	266 (34.9)
Negative	478 (62.6)
Unknown	19 (2.5)
Histological grade	
Grade 1	95 (12.5)
Grade 2	318 (41.7)
Grade 3	328 (42.9)
Unknown	22 (2.9)
ER	
Positive	269 (35.3)
Negative	103 (13.5)
Unknown ^a	391 (51.2)
PgR	
Positive	225 (29.5)
Negative	147 (19.3)
Unknown ^a	391 (51.2)

^aTx and unknown receptor status included patients who underwent diagnostic biopsy at another local clinic.

had not been performed. Survival curves were obtained by the Kaplan-Meier method [8] and differences between the survival curves were investigated using the log-rank test [9]. Differences were regarded as statistically significant at $P < 0.05$.

RESULTS

The clinicopathological characteristics of the patients are shown in Table I. The median age of the patients at initial surgery was 52 years (range 21–85 years). The median follow-up period for patients known to have sur-

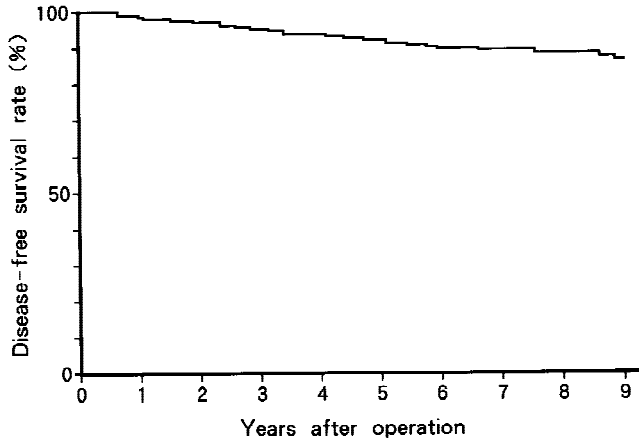


Fig. 1. DFS curves for 763 node-negative invasive breast cancer patients.

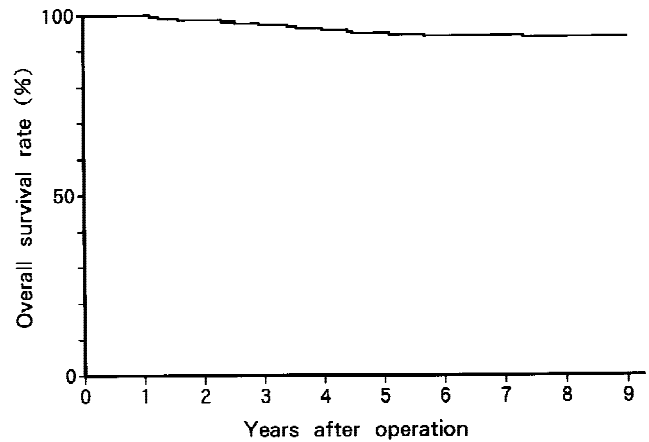


Fig. 2. OS curves for 763 node-negative invasive breast cancer patients.

vived was 74 months after initial surgery, ranging from 15 to 121 months. As shown in Figure 1, at 5 and 7 years, the respective DFS rates for all node-negative invasive breast cancer patients were 90.8% and 87.8%, whereas their OS rates were 93.9% and 93.2%, respectively (Fig. 2). Differences in DFS and OS rates after stratification by pathological tumor size of invasive component are shown in Figures 3 and 4, respectively. Patients with a pathological tumor size of invasive component of more than 2 cm (319 patients) had a statistically significantly lower DFS than those with tumors measuring 2 cm or less (361 patients) ($P = 0.045$), although the difference in OS did not reach significance ($P = 0.350$). Hormone receptor status contributed to a marginal difference in OS ($P = 0.078$), but not in DFS ($P = 0.485$) (Figs. 5, 6). Patients with positive hormone receptor status (ER and/or PgR positive) (280 patients) tended to have a better OS than those negative for both types of hormone receptor (92 patients) ($P = 0.078$). However, as shown in Figures 7 and 8, patients with tumors of histological grade 3 (328 patients) had a much poorer prognosis than those with tumors of histological grade 1 or 2 (413 patients) ($P = 0.008$ for OS and $P = 0.042$ for DFS). The 5-year DFS and OS rates for patients with histological grade 3 tumors were 88.4% and 91.4%, respectively, while those for patients with histological grade 1 or 2 tumors were 91.4% and 95.6%, respectively. Furthermore, the respective 5-year DFS and OS rates for patients with histological grade 3 tumors larger than 2 cm in pathological tumor size of invasive component (195 patients) were 85.5% and 87.6%, indicating that this subpopulation of node-negative invasive ductal carcinoma patients is at high risk for recurrence. However, lymphatic invasion by tumor cells was not related to patient survival (data not shown). The initial sites of recurrence were local skin lesions (10 patients; 10/49: 20.4%), locoregional lymph nodes (5 patients; 5/49: 10.2%), bone (12 patients; 12/49: 24.5%), lung and pleura (20 patients; 20/49: 40.8%), and

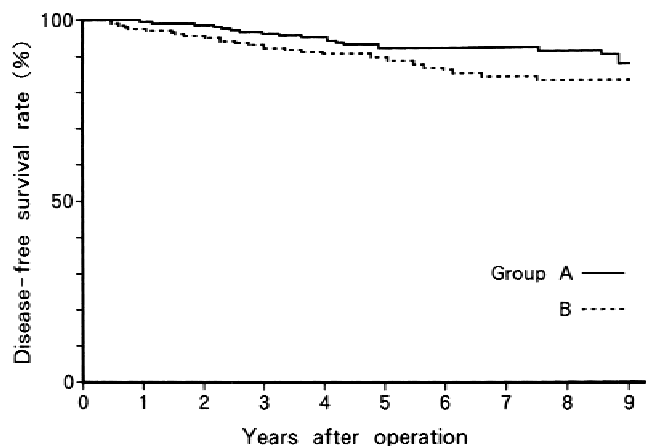


Fig. 3. DFS curves for node-negative invasive breast cancer patients, stratified by pathological tumor size of invasive component. Group A: $t \leq 2.0$ cm (361 patients); group B: $t > 2.0$ cm (319 patients) ($P = 0.045$).

liver (2 patients; 2/49: 4.1%). Thirty-two patients have been found to have developed second primary malignancies, including 10 with contralateral breast cancers, during follow-up after initial surgery. These patients were also included in the survival analyses.

DISCUSSION

The prognosis of breast cancer patients, particularly those with node-positive disease, has recently improved [1–3]. However, it is likely that the outcome of treatment for node-negative breast cancer has reached a plateau. The proportion of node-negative invasive breast cancer patients who can be cured by adjuvant therapies remains controversial [1–3], mainly because useful prognostic factors have not been established for node-negative patients. We have already reported that histological grade, combined with examinations for the presence of certain gene and chromosomal alterations, is effective in identi-

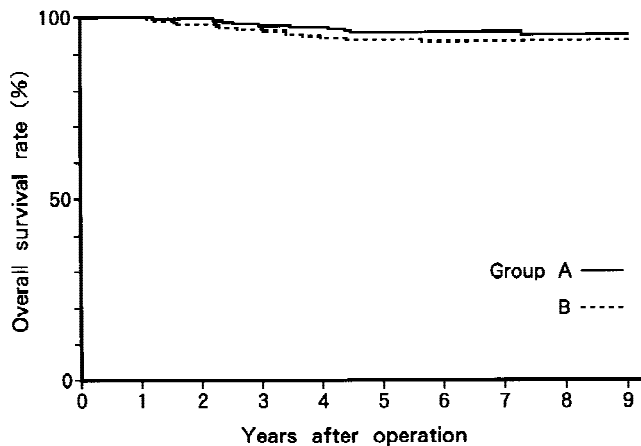


Fig. 4. OS curves for node-negative invasive breast cancer patients, stratified by pathological tumor size of invasive component. Group A: $t \leq 2.0$ cm (361 patients); group B: $t > 2.0$ cm (319 patients) ($P = 0.350$).

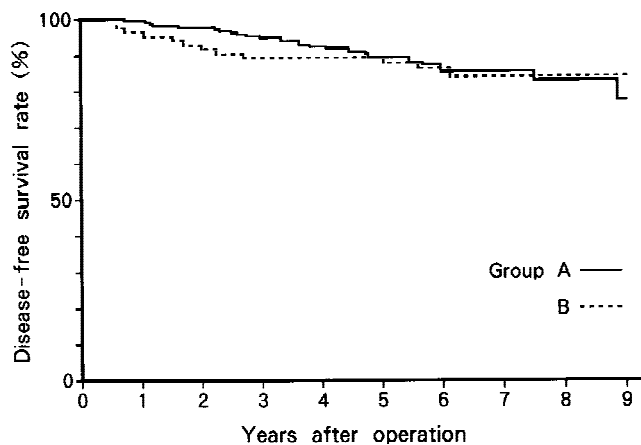


Fig. 5. DFS curves for node-negative invasive breast cancer patients, stratified by hormone receptor status. Group A: ER and/or PgR positive (280 patients); group B: both ER and PgR negative (92 patients) ($P = 0.485$).

fying node-negative breast cancer patients at high risk of early recurrence [10,11]. However, in this previous study, the number of patients was small, the methods used to evaluate genetic alterations were a little complicated for routine use in a community hospital, and the follow-up period was relatively short (mean follow-up period: 43 months) [11].

In the present study, to exclude the effects of postoperative adjuvant chemotherapy, we evaluated a large series of consecutive node-negative breast cancer patients over a long follow-up period (median: 74 months) at a single institute. At 5 years, the respective DFS and OS rates for node-negative invasive breast cancer patients were 90.8% and 93.9%. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that 5-year DFS and OS rates of all node-negative breast cancer patients were 67–84% and 81–89%, respectively

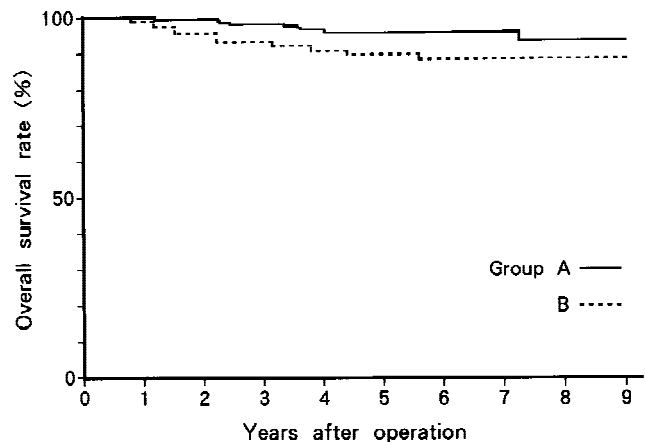


Fig. 6. OS curves for node-negative invasive breast cancer patients, stratified by hormone receptor status. Group A: ER and/or PgR positive (280 patients); group B: both ER and PgR negative (92 patients) ($P = 0.078$).

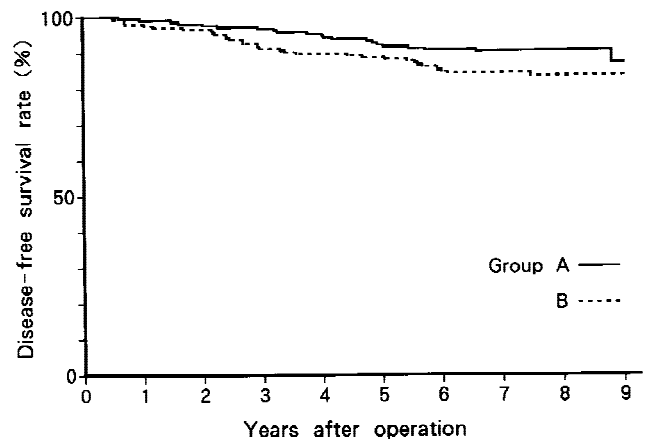


Fig. 7. DFS curves for node-negative invasive breast cancer patients, stratified by histological grade. Group A: histological grade 1 or 2 (413 patients); group B: histological grade 3 (328 patients) ($P = 0.042$).

[2,3]. These data indicate a better treatment outcome for node-negative invasive breast cancer patients in Japan than in Western countries, regardless of the effects of adjuvant chemoendocrine therapies. We think that breast cancers in Japanese women are biologically less aggressive, although there is no direct evidence for this hypothesis. Considering the relatively low incidence of breast cancer in Japan, certain genetic and/or environmental factors could contribute to these ethnic differences in breast carcinomas [12].

With regard to clinicopathological prognostic factors, pathological tumor size of invasive component was related only to DFS in our patients, whereas hormone receptor status had a marginal impact on their OS, but was not related to their DFS. These differences might be partly explained by the fact that patients with positive hormone receptor status were treated with endocrine therapy after relapse. These data suggest that hormone

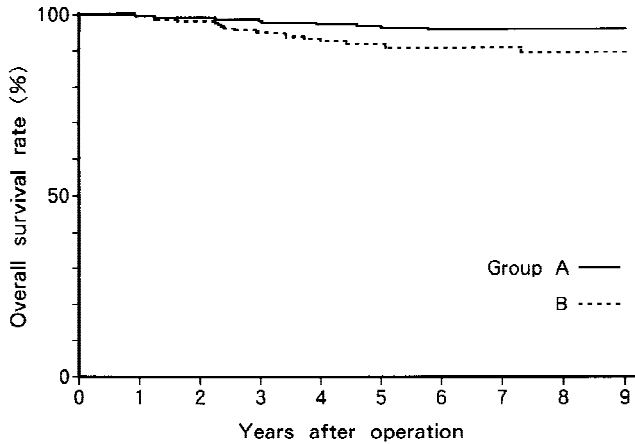


Fig. 8. OS curves for node-negative invasive breast cancer patients, stratified by histological grade. Group A: histological grade 1 or 2 (413 patients); group B: histological grade 3 (328 patients) ($P = 0.008$).

receptor status is not a prognostic factor but a predictive factor, which can be used to identify patients sensitive to endocrine therapy.

The present study also confirmed the prognostic value of histological tumor grade in node-negative breast cancer patients. As we reported previously, p53 mutations or c-erbB-2 amplifications occurred almost exclusively in histological grade 3 tumors [10,13]. Although the ethnic differences of breast cancer might exist, our data cast doubt on the use of tumor size or hormone receptor status alone as an indication for adjuvant therapy in node-negative invasive breast cancer patients. In this study, histological grade was the most reliable prognostic factor in this population, particularly when combined with pathological tumor size of invasive component. The 5-year DFS and OS rates of patients with histological grade 3 tumors larger than 2 cm in pathological tumor size of invasive component were close to those of node-positive patients treated with adjuvant chemotherapy [14]. We therefore consider adjuvant chemotherapy to be justified in node-negative invasive breast cancer patients with histological grade 3 tumors, and since 1994, adjuvant chemoendocrine therapy has been administered to node-negative patients with histological grade 3 tumors in a multicenter prospective randomized trial setting [15].

In conclusion, when compared with their Caucasian counterparts, Japanese invasive breast cancer patients without lymph node metastasis show an approximate

5–10% 5-year survival advantage, regardless of prognostic factors and the effects of adjuvant therapies. Histological tumor grade appears to be the most useful prognostic factor in this population.

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